UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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APR 22 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 707-EUP-RRG/7G3479/7H5523. RH-3866 (Rally™) Fungicide. Petition for Temporary Tolerances for Processed Commodities of Apples and Grapes, and Meat, Milk and Eggs.

Tox. Chem. No. 723K
Project No. 7-0339

TO: Lois A. Rossi, PM Team #21
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Record Nos. 184147, 185728, 185729

Background and Request:

Rohm and Haas has submitted a petition for the establishment of temporary tolerances for RH-3866 residues in or on processed commodities of apples and grapes, and meat, milk and eggs. These proposed tolerances are in addition to the temporary tolerance of 0.5 ppm which EPA established on February 28, 1986 for the raw agricultural commodities, apples and grapes (fresh market only) (see memorandum from J.E. Harris to H. Jacoby, dated 2/12/86 for details of EUP on RH-3866 40W, proposed temporary tolerance and Toxicology Branch comments). The EUP on RH-3866 40W contained an annual use of 2454 pounds active ingredient (a.i.) of which 54%, 36% and 21% was to be used on apples, grapes and perennial grasses grown for seed, respectively, for approximately 1620 acres. The Registrant claims that the existing EUP for Rally™ 40W fungicide and a proposed EUP for Rally™ 60DF fungicide will involve uses which may lead to residues occurring in the raw agricultural commodity which will enter the food and/or feed chain (the EUP for Rally™ 60DF fungicide and the supporting toxicity data were reviewed by the Registration Division - see memorandum from D. Graham to L. Rossi, dated 1/13/86; the proposed amount

of active ingredient to be used for the EUP was 808 pounds. This amount will not exceed the amount of active ingredient authorized under the EUP for the 40W formulation (because a compensating reduction in the a.i. requirement for the 40W EUP program will be made). Therefore, the Registrant is requesting a removal of the fresh market restriction on current labels, thereby allowing treated crops to freely enter all channels of trade. The following temporary tolerances are proposed:

Commodity		Parts per Million
Apples:	Wet Pomace	1.0 ppm
	Dry Pomace	5.0 ppm
Grapes:	Wet Pomace	1.0 ppm
	Dry Pomace	5.0 ppm
	Raisins	5.0 ppm
	Raisin Waste	12.5 ppm
Meat and Meat By-Products (except liver)		0.04 ppm
Liver (cattle, goats, hogs, horses or sheep)		0.5 ppm
Milk		0.1 ppm
Eggs		0.04 ppm

Response:

The Toxicology Branch has no objection to allowing the proposed additional temporary tolerances for RH-3866 residues provided that the Registrant submits the additional data requested by the Registration Division for the EUP on Rally™ 60 DF Fungicide (see memorandum from D. Graham to L. Rossi, dated 1/13/87). The following comments discuss changes that have been made in the PADI value since the EPA established the original tolerance on February 28, 1986, and summarize the available toxicity data base on RH-3866 Technical, RH-3866 40W Fungicide and RH-3866 60DF Fungicide required to support this petition.

In a memorandum from J.E. Harris to H. Jacoby, dated 2/12/86, the Toxicology Branch (TB) considered the data adequate to support temporary tolerances for RH-3866 40W Fungicide for apples and grapes at 0.5 ppm (707-EUP-RNL) and for RH-3866 40W on perennial turf grown for seed (707-ROG) with restrictions on grazing of livestock. In the memorandum, a provisional acceptable daily intake (PADI) was calculated from a preliminary report on a 1-year dog study. The PADI was set at 0.0025

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mg/kg bodyweight/day (using a NOEL of 2.5 mg/kg bodyweight/day with a 1000-fold safety factor). The ADI Committee of the Toxicology Branch has decided to temporarily change the PADI, using the completely evaluated subchronic dog study until the chronic studies (recently submitted with a separate petition) can be fully evaluated. Therefore, since the NOEL for the subchronic dog study is 0.3 mg/kg bodyweight/day based upon centrilobular or mid-zonal hepatocellular hypertrophy, the PADI is set at 0.0003 mg/kg bodyweight/day (using a 1000-fold safety factor).

The following toxicity studies are recommended to be submitted in support of the proposed temporary tolerance (ref. EPA Pesticide Assessment Guidelines Subdivision I - Experimental Use Permits, October, 1982). Those recommendations that have been satisfied are indicated:

	Required	Satisfied
Technical Product		
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Gene mutation	Yes	Yes
Chromosome aberrations	Yes	Yes
Other genotoxic effects	Yes	Yes[1]
90-day subchronic oral		
rodent	Yes	Yes
nonrodent	Yes	Yes
Teratology (1 species)	Yes	Yes
2-Generation reproduction	Yes	Yes
One-Year or longer interim report on chronic feeding	Yes[2]	Yes[2]
End-Use Product: RH-3866 40W		
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Acute inhalation LC_{50}	Yes	Yes

	Required	Satisfied
Eye irritation	Yes	Yes[1]
Dermal irritation	Yes	Yes
Dermal sensitization	Yes	No[3]
End-Use Product: RH-3866 60DF		
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Acute inhalation LC_{50}	Yes	No[4]
Eye irritation	Yes	Yes
Dermal irritation	Yes	No[4]
Dermal sensitization	Yes	No[4]

Footnotes for Table:

1. A mutagenicity study on the potential of technical RH-3866 to induce other genotoxic effects and a repeat eye irritation study for the 40W formulation were submitted with other petitions relating to these formulations. The two studies were reviewed in order to respond to this petition and were found to be acceptable studies.

2. A one-year or longer interim report on a chronic feeding study is required in cases where the TMRC of all treated crops exceeds 50% of the MPI. Since this subject is being addressed by the Residue Chemistry Branch and since preliminary data are available on a chronic feeding study in dogs, it is being included here.

3. The dermal sensitization study for the 40W formulation was waived by TB for the EUP on this formulation on the basis of a negative dermal sensitization study on a 24% formulation (see memo from J. Harris to H. Jacoby, dated 2/12/86). This study will be required for Registration.

4. The data requirements for these studies are being addressed by the Registration Division (RD) in response to an EUP petition for the 60DF formulation.

The Registrant requested a waiver of the acute inhalation study on the Technical product on the basis that the chemical is a solid with a low vapor pressure. TB is not requiring this study for the issuance of this temporary tolerance. However, the study may be required for Registration.

The proposed labelling for the 40W formulation should be changed to reflect the fact that the eye irritation study has placed this formulation in Toxicity Category II. The CAUTION statement should be changed to WARNING as it is with the 60DF formulation.

Studies Reviewed

Study	Results	Core Classification
.....Technical.....		
Mutagenicity - Unscheduled DNA Synthesis (In Vitro)	Negative. Tested up to toxic levels (1000 micrograms/ml)	Acceptable
.....40 WP.....		
Eye Irritation	Moderately irritating to the eye. Maximum score 17.1; irritation clearing in 8-21 days. Toxicity Category II.	Guideline

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8-Point Review

[Prepared for 707-EUP-RRG; 7G3479; 7H5523, RH-3866 on apples, grapes, meat and meat by-products, milk and eggs, April 13, 1987]

1. Toxicity data with technical grade RH-3866 considered in support of these tolerances (selected studies).

Acute oral LD_{50}, rat	1.6 g/kg in males 2.3 g/kg in females
90-day feeding, rat	NOEL: 50 mg/kg/day; LEL: 150 mg/kg/day increased liver, kidney wts.; hypertrophy, necrosis in liver; pigmentation in convoluted kidney tubules
13-week oral, dog	NOEL: ~~2.5~~ 0.3 mg/kg/day, males; 5 mg/kg/ day, females; LEL: 5 mg/kg/day, males; (20 mg/kg/day), females. Hepatic hypertrophy in both sexes, incr. AP in both sexes.
2-Generation reproduction, rat	Systemic NOEL: 4 mg/kg/day; LEL: 16 mg/kg/day, incr. liver wts., hepatic hypertrophy in males. Reproductive NOEL: 16 mg/kg/day. LEL: 80 mg/kg/day, testicular, epididymal and prostatic atrophy in F_2 males, incr. stillborns, decr. bdywt. gain in pups during lactation in F_1 and F_2.
Teratology, rat	Teratogenic NOEL: > 469 mg/kg/day (HDT) Maternal NOEL: 313 mg/kg/day LEL: 469 mg/kg/day (decr. bdywt. gain, clinical signs) Embryotoxic NOEL: 31 mg/kg/day LEL: 94 mg/kg/day (incr. resorptions and decreased viability index) Fetotoxic NOEL: 94 mg/kg/day LEL: 313 mg/kg/day (incr. 7th cervical + 14th rudimentary ribs)
One-Year Feeding, dog preliminary report	NOEL: 2.5 mg/kg/day, LEL: 10 mg/kg/day hepatic hypertrophy in both sexes, incr. liver wts in females.

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Mutagenicity Studies

Reverse mutation assay (Ames), point mutation in CHO/HGPRT cells, *in vivo* cytogenetic assay and unscheduled DNA synthesis. All the tests were negative and acceptable.

2. Additional toxicity data considered desireable: None for a temporary tolerance

3. No requests for additional data have been made.

4. A temporary tolerance of 0.5 ppm for the raw agricultural commodities, apples and grapes (fresh market only) has been issued.

5. The relationship of these tolerances on the contribution to the diet and the MPI must be addressed by the Residue Chemistry Branch and the TAS system.

6. The subchronic dog feeding study with a safety factor of 1000 was used to calculate the PADI. The NOEL was 0.3 mg/kg/day. The PADI is calculated to be 0.0003 mg/kg/day and MPI is calculated to be 0.0180 mg/day.

7. There are no pending regulatory actions against registration of the pesticide.

8. None.

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Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation - Rabbit (81-4)

TOX. CHEM. NO.: 723K

ACCESSION NUMBER: 266026

TEST MATERIAL: RH-53,866 WP 40 Fungicide

SYNONYMS: Rally, Systhane, Nova

REPORT NUMBER: 86R-0193

SPONSOR: Rohm and Haas Company

TESTING FACILITY: Rohm and Haas Company, Philadelphia, PA

TITLE OF REPORT: RH-3866 40WP: Definitive Rabbit Eye Irritation in Males

AUTHOR(S): A.S. Romanello

REPORT ISSUED: October 21, 1986

IDENTIFYING VOLUME: Volume 1 of 10

CONCLUSION: RH-53,866 is moderately irritating to the eye. The maximum total mean irritation score was 17.1, with the irritation clearing in 8-21 days.

Toxicity Category: II

Classification: Core Guideline

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: 1-(2-cyano-2(4-chlorophenyl)hexyl)-1H-1,2,4-triazole
Description: yellowish-white powder
Batch #(s), Other #(s): Lot EG-0809-1
Purity: 44%
Source: Rohm & Haas
Vehicle (if applicable): None

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): New Zealand White Rabbit (Male)
Age: Not given
Weight(s): Not given
Source(s): Hazleton Res. Animals

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3. Procedures:

RH-53,866 40 WP was tested for eye irritation potential using the Draize test. Six animals were used for testing the compound with unwashed eyes and 3 animals were used for testing with washed eyes. One day prior to the test, the eyes of all the animals were examined for abnormalities using sodium fluorescein. For the test, 1/10 gm of the test material was instilled into the conjunctival sac of one eye of each rabbit and the lids were held closed for a moment. Sodium fluorescein was used to aid in the examinations of the eyes. The animals were examined at 24, 48, and 72 hours and at 7 and 14 days and scored according to the Draize method.

B. RESULTS:

The highest total mean irritation value was 17.1. The irritation still persisted at 7 days but cleared by day 14. In addition, although the investigators gave a score of zero to two animals at day 7 for corneal involvement, they noted that parts or all of the corneas of these animals appeared hazy after treatment with sodium fluorescein and that it was considered to be related to treatment. This had also disappeared by day 14. Therefore, the results from this study place this chemical in the category of moderately irritating, Toxicity Category II.

C. DISCUSSION:

The design of this study places it in the Core Guideline Category, but it should be noted that there was insufficient explanation of the reactions. Only a table was submitted with the results for each individual animal. In addition, for several animals, a footnote was provided which stated that the cornea or a part of the cornea was hazy and it was considered to be related to treatment. No explanation was given as to why a score was not given for this effect.

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DATA EVALUATION REPORT

STUDY TYPE: In Vitro Unscheduled DNA Synthesis (84-2)

TOX. CHEM. NO.: 723K

ACCESSION NUMBER: 266100

TEST MATERIAL: RH-53,866 Technical

SYNONYMS: Rally, Systhane, Nova, Myclobutanil

REPORT NUMBER: 86R-084

SPONSOR: Rohm & Haas Company, Philadelphia, PA

TESTING FACILITY: Rohm & Haas Company, Toxicology Dept., Spring House, PA

TITLE OF REPORT: RH-53,866 Technical In Vitro Unscheduled DNA Synthesis Assay

AUTHOR(S): G. Muller

REPORT ISSUED: 7/22/86

IDENTIFYING VOLUME: Volume 26 of 47

CONCLUSION: RH-53,866 did not induce an increase in unscheduled DNA synthesis under the conditions of the bioassay.

Classification: ACCEPTABLE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: alpha-butyl-alpha-(4-chlorophenyl)-1H-1,2,4-triazole-1-propanenitrile
Description: Not given
Batch #(s), Other #(s): TD No. 86-37, lot # 83159-5
Purity: 91.9%
Source: Rohm & Haas
Vehicle (if applicable): DMSO
Positive Control(s) (if applicable): 2-acetylaminofluorene

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): CRCD (Crl:CD BR) male rat
Age: Not given
Weight(s): Not given
Source(s): Charles River Labs, Lakeview, NJ

3. Procedures:

Hepatocytes from freshly perfused rat liver were prepared and dispensed into a series of 6-well Linbro dishes (1 dish/dose). Each well contained a plastic coverslip. Following attachment, the cells were exposed to a medium containing 10 microcuries/ml tritiated thymidine and either the test compound, the positive control, DMSO or the negative control (no treatment) for 18 to 20 hours. Ten concentrations of the test compound were assayed, ranging from 0.1 micrograms/ml to 1000 micrograms/ml. One coverslip from each treatment concentration was used for toxicity assessment. The remaining coverslips were washed, swelled in hypotonic solution and fixed using an ethanol-acetic acid solution. The coverslip cultures that were to be used for autoradiography were fixed, mounted cell-side up onto microscope slides, and dipped in photographic emulsion for approximately 7 days. Following development, the slides were stained. On the basis of the toxicity assessment, the slides from the 5 test compound concentrations were selected for scoring of unscheduled DNA synthesis (UDS) along with the positive, negative and untreated controls. Treatment groups with less than 50% survival after treatment were not scored for UDS. Fifty cells from each of 3 slides for each treatment group with sufficient cell survivors were scored for the number of silver grains over both the nucleus and cytoplasm. The net nuclear grain count for each cell and the mean net nuclear grain count for each slide were determined. UDS was measured by comparing the results from the treated groups with the control groups.

The assay was considered acceptable for evaluation if the following criteria were met: the values for the untreated or solvent controls were consistent with values of recent historical controls, the positive control values indicated that the cultured cells were capable of metabolic activation and the slides from at least 2 treatment groups were scorable for UDS and had greater than 50% survival 24 hours following treatment. The results were considered to be positive if a reproducible significant increase in nuclear grains when compared to the solvent and negative controls was observed. Conclusive negative results must include three test concentrations, with at least two of the concentrations having greater than 75% cell survival 24 hours following treatment. One of the test concentrations must have shown some indication of toxicity or have been the nearest test concentration to a test concentration that could not be scored for UDS due to excessive toxicity.

B. RESULTS:

Based upon the toxicity assessment, the following treatment levels were scored for UDS: 0.1, 0.5, 1.0, 5.0 and 10 micrograms/ml. In addition, the DMSO solvent control, the untreated control and a single concentration of 2-AAF (0.2 micrograms/ml) were scored for UDS. No increases in UDS when compared to the negative and solvent controls were observed in any of the treated cultures. The results from the positive control indicated that the cells were capable of metabolic activation and DNA repair in response to DNA damage. The following tables summarize the response from the assay.

C. DISCUSSION:

The assay appears to have been well conducted. It is ACCEPTABLE as written.

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